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<p>(51) International Patent Classification <sup>5</sup> : A61K 31/70, A23L 1/304, 1/305 A23L 1/09, 2/26, A23G 3/00 A23L 1/06</p>	<p>A1</p>	<p>(11) International Publication Number: <b>WO 92/15311</b>  (43) International Publication Date: 17 September 1992 (17.09.92)</p>
<p>(21) International Application Number: PCT/EP92/00369 (22) International Filing Date: 21 February 1992 (21.02.92)  (30) Priority data: MI91A000553 1 March 1991 (01.03.91) IT  (71) Applicant (for all designated States except US): DEPHA TEAM S.R.L. [IT/IT]; Via Cassanese, 224, Palazzo Tiep- olo, I-20090 Segrate (IT).  (72) Inventors; and (75) Inventors/Applicants (for US only) : PALAZZI, Camillo, Maria, Francesco, Giulio [IT/IT]; PROCIDA, Carla [IT/IT]; RONCHI, Celestino [IT/IT]; CESCHEL, Gian- carlo [IT/IT]; Via Cassanese, 224, Palazzo Tiepolo, I- 20090 Segrate (IT).</p>		<p>(74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettu- ale, Via Rossini, 8, I-20122 Milano (IT).  (81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European pa- tent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (Euro- pean patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.  Published With international search report.</p>
<p>(54) Title: DIETETIC OR PHARMACEUTICAL COMPOSITIONS FOR THE RESTORATION OF ADENINE NUCLEO- TIDE CELL CONTENT IN SKELETAL AND CARDIAC MUSCLES  (57) Abstract  Dietetic or pharmaceutical compositions containing a (D)-ribose and magnesium (L)-aspartate mixture for use as nutri- tional integrators are herein described.</p>		

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DIETETIC OR PHARMACEUTICAL COMPOSITIONS FOR THE  
RESTORATION OF ADENINE NUCLEOTIDE CELL CONTENT IN  
SKELETAL AND CARDIAC MUSCLES

The present invention relates to dietetic or pharmaceutical compositions containing a mixture of (D)-ribose and magnesium (L)-aspartate in various ratios.

5        One of the most important problems in the skeletal and cardiac muscle physiopathology is to restore, or to maintain adenine nucleotide cell content within physiological limits during or after a prolonged and/or exhausting physical effort, by a necessary or advisable  
10        nutritional intervention. On the contrary, the balance between energy requirement and energy availability would be jeopardized. This unfavourable situation occurs when dephosphorylation of ATP into ADP, and subsequently into AMP, continues till adenosine,  
15        inosine and ipoxanthine production.

These products are released by the cell (R.M. Berne; Am. J. Physiol., 204,317,1963), and therefore are lost for the purpose of a possible restoration of adenine nucleotides.

20        Theoretically, the problem of adenine nucleotide degradation could be solved by means of some biochemical-nutritional possibilities, for example, administration of adenosine (K. Reibel and M.J. Rovetto; Am. J. Physiol., 237,247,1979) or inosine  
25        (V.T. Wiedmeier, R. Rubio and R.M. Berne; J. Mol. Cell. Card.; 4,445,1972), which however proved to be rather ineffective.

It has now been found that the administration of (D)-ribose surprisingly enhances adenine nucleotide synthesis, thus resulting in a higher availability of 5-phosphoribosyl-1-pyrophosphate, which is the limiting factor of adenine nucleotide biosynthesis. Accordingly, administration of (D)-ribose prevents and reduces adenine nucleotide decrease in muscles during strong stress conditions.

Therefore, dietetic or pharmaceutical compositions containing (D)-ribose, optionally combined with magnesium (L)-aspartate, are an object of the present invention.

In fact, it is well known that about 55% magnesium ions in the human body are located in the bones, while the remaining are in the soft tissues. A decrease in muscle  $Mg^{2+}$  has particularly been observed during magnesium deficiency and during intense physical exercises.

Magnesium ion mobilization, particularly the loss thereof from muscle cells during physical exercise, can be explained by the high activity of the  $Mg^{2+}$  dependent enzymes, which are involved in the energy metabolism (creatinine phosphokinase, glycogen phosphorylase and myosin ATPase). The correlation between  $Mg^{2+}$  loss and exercise intensity can depend on: i) a reduced kidney concentrating capacity which is induced directly by the physical exercise or indirectly by the increase of the hormones inducing  $Mg^{2+}$  ion tubular reabsorption (aldosterone, antidiuretic hormone, thyroid hormones) whose hematic concentration can remain high up to 14 hours after the end of the physical exercise; ii)

acidosis, due to lactate accumulation, which can induce magnesiuria through a decrease in magnesium tubular reabsorption.

Accordingly, the (D)-ribose and magnesium (L)-aspartate combination assures a correct adenine nucleotide increase and, at the same time, allows to balance muscle  $Mg^{+2}$  concentration both in magnesium deficiencies and during physical exercises. Administration of the compositions of the present invention is also useful in pathologic conditions wherein a prompt restoration of weary muscles is necessary, for example in diabetes, alcoholism, cardiopathies, pregnancy.

The dietetic compositions of the present invention can contain from 200 to 2000 mg of (D)-ribose. When present in the composition, the magnesium (L)-aspartate unitary dose can range from 100 to 1000 mg. Weight ratios of (D)-ribose to magnesium (L)-aspartate are not critical and will generally range from 1:1 to 5:1.

The compositions of the present invention can further contain other active ingredients or integrators with adjuvant, complementary or useful activities.

Examples of said elements which are profitably used are:

- mineral salts and/or vitamins
- potassium aspartate.

The dietetic or pharmaceutical compositions of the invention can be prepared according to conventional techniques and excipients. Said compositions are prepared by admixing (D)-ribose and magnesium (L)-aspartate with physiologically acceptable excipients

having pleasant appearance, smell and taste.

Examples of excipients known in the food industry are diluents, sweeteners, binders, flavoring aids, lubricants and non-sticking agents, natural and  
5 artificial food dyes.

Examples of diluents are: microcrystalline cellulose, glycine, lactose; maize, potatoes and rice starch; mannitol, sorbitol, sucrose, fructose; examples of sweeteners are: saccharin sodium, saccharin acid,  
10 aspartame, honey; examples of binders are: starch, polyvinylpyrrolidone, polyvinyl alcohol, hydroxymethylcellulose; examples of flavor aids are: citric acid and the salts thereof, tartaric acid and the salts thereof, sodium glutamate, sodium chloride,  
15 orthophosphoric acid and the salts thereof, menthol; examples of lubricants and non-sticking agents are: magnesium stearate, talc, 200 to 6000 PEGs (polyethylene glycols), glyceryl behenate, glycerin, mineral oil, silicone oils, levynite; examples of food  
20 dyes are: chlorophyll, bilberry anthocyanins; E104, E110; titanium dioxide, iron oxides; examples of dietetic compositions are: chewable, effervescent or swallowable tablets, syrups, fruit beverages, soluble granulate sachets, fruit jellies, candies.

25 The following examples further illustrate the invention.

#### EXAMPLE 1

##### Chewable tablets

1 Tablet contains

30	(D)-Ribose	mg	200
	Magnesium (L)-aspartate	mg	200

5

Maize starch	mg	50
Lactose	mg	50
Magnesium stearate	mg	5

EXAMPLE 25 Drinkable solution

250 ml of solution contain:

(D)-Ribose	mg	1000
Magnesium (L)-aspartate	mg	1000
Sorbitol	mg	30
10 Citric acid	mg	50
Sodium chloride	mg	50
Methyl-p-hydroxybenzoate	mg	45
Propyl-p-hydroxybenzoate	mg	5
Purified water q.s. to	ml	250

15

EXAMPLE 3Granulate sachet

1 Sachet contains:

(D)-Ribose	mg	1000
Magnesium (L)-aspartate	mg	500
20 Lactose	mg	200
Methylcellulose	mg	10
Tartaric acid	mg	5
Lemon flavor	mg	25
Sorbitol q.s. to	g	3

25

EXAMPLE 4Chewable tablets

1 Tablet contains:

(D)-Ribose	mg	500
Magnesium (L)-aspartate	mg	500
30 Mannitol q.s. to	g	1,5
Polyvinylpyrrolidone	mg	50

6

	Citric acid	mg	10
	Sodium chloride	mg	3
	Orange flavor	mg	20
	Magnesium stearate	mg	10
5	Talc	mg	8

EXAMPLE 5Chewable tablets

1 Tablet contains:

	(D)-Ribose	mg	800
10	Mannitol q.s. to	g	1,5
	Polyvinylpyrrolidone	mg	100
	Citric acid	mg	10
	Sodium chloride	mg	3
	Orange flavor	mg	20
15	Magnesium stearate	mg	10
	Talc	mg	8

EXAMPLE 6Sugar pills

1 Sugar pill contains:

20	(D)-Ribose	mg	500
	Magnesium (L)-aspartate	mg	100
	Maize starch	mg	50
	Talc	mg	30
	Levylite	mg	25
25	Magnesium stearate	mg	5
	Sucrose	mg	150
	Ell0	mg	0,025
	Carnauba wax	mg	0,001



CLAIMS

1. Dietetic or pharmaceutical compositions containing (D)-ribose as active ingredient.
- 5 2. Dietetic or pharmaceutical compositions according to claim 1 further containing magnesium (L)-aspartate.
3. Dietetic or pharmaceutical compositions according to claim 1 or 2 containing from 200 to 2000 mg of (D)-ribose and from 100 to 1000 mg of magnesium (L)-  
10 aspartate.
4. Dietetic or pharmaceutical compositions according to anyone of the preceding claims, containing other active ingredients or integrators with adjuvant, complementary or anyway useful activities.
- 15 5. Dietetic or pharmaceutical compositions according to claim 4, further containing at least another active ingredient or integrator selected from the group consisting of mineral salts, vitamins and potassium aspartate.
- 20 6. Dietetic or pharmaceutical compositions according to anyone of the preceding claims, in the form of effervescent, chewable and swallowable tablets, syrups, fruit drinks, soluble granulate sachets, fruit jellies, candies.

## INTERNATIONAL SEARCH REPORT

PCT/EP 92/00369

International Application No

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61K31/70; A23L2/26;	A23L1/304; A23G3/00;	A23L1/305; A23L1/06; A23L1/09
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	A61K ; A23L	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	EP,A,0 324 227 (RONCARI, RAYMOND A.) 19 July 1989 see abstract; claims 1-6 ---	1,6
A	US,A,4 824 660 (DEBRA A. ANGELO & RICHARD A. WILSON) 25 April 1989 see abstract; claims 1,2 ---	1,6
A	FR,A,2 609 397 (LABORATOIRES SEROBIOLOGIQUES) 15 July 1988 see abstract; claims 1,2,5 ---	1-6
<p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
19 MAY 1992	02.06.92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	LEHERTE C.F.M.	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO. EP 9200369  
SA 56433**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on  
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0324227	19-07-89	US-A- 4871718	03-10-89
		AU-A- 1769088	29-06-89
		JP-A- 1175939	12-07-89
		US-A- 4923851	08-05-90
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US-A-4824660	25-04-89	None	
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FR-A-2609397	15-07-88	None	
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82